REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office Action dated November 27, 2001 are respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page(s) is/are captioned "**Version with markings to show changes made.**"

I. Amendments

Claims 1 and 2 are amended to recite that the step of inactivating is carried out before the step of purifying, and that the purifying is conducted by physical means. Support for these amendments can be found on page 6, line 12 and on page 11, lines 28-29.

Claims 5 and 13 are amended to recite that the inactivation is carried out in a range of about 4°C to 10°C. Support for these amendments can be found in point (5) on page 5 of the specification.

New dependent claims 17 and 18 are added to specify that the appearance of the surface or envelope layer of the particle structure, based on electron microscopic analysis, is rough or fuzzy. Support for this can be found on page 8, lines 3-6.

The abstract is amended to provide a brief narrative of the disclosure as embodied by claim 1.

Accordingly, no new matter has been added by these amendments.

II. Objection to claims

The Examiner objected to claims 5 and 13 for the informality that the cited range is 40-100 degrees Celcius, however the specification cites 4-10 degrees Celcius.

Claims 5 and 13 are amended to recite that the inactivation is carried out in a range of about 4°C to 10°C. Accordingly, Applicants respectfully request withdrawl of the objection.

III. Specification

The Examiner reminded Applicants of the proper content of an abstract. Applicants have amended the abstract to provide a brief narrative of the disclosure as a whole.

IV. Rejections under 35 U.S.C. §102

Claims 1-7, 9, and 11-16 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Huiying et al. (Virologica Sinica, 13(3):9-13, 1998, hereinafter "Huiying, et al. (1998)") or Takegami et al. (Antiviral Research, 37:37-45 , 1998).

Claims 1-7, 9, and 11-16 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Huiying et al. (Virologica Sinica, 10(4):273-277 , 1995, hereinafter "Huiying et al. (1995)").

A. The Present Invention

The present invention relates to an inactivated virus particle, as a reinforced immunogen, prepared from a culture of cells infected with virus belonging to a group of Japanese encephalitis viruses. The process of preparation comprises a step of inactivation followed by a step of purification by physical means wherein a neutralizing antibody titer of the anti-serum obtained by immunization with the virus particles is about twice to about 10 times the neutralizing antibody titer of the anti-serum obtained by immunization with inactivated virus particles prepared from virus cultured in mouse brain. The effect of the providing the step of inactivation before the step of purification and that the purification is by physical means viruses can be purified in a state such that the surface of the virus is not changed and the antigen is provided in the correct steric conformation for the antigen to react well with the antibodies.

B. The Prior Art

HUIYING ET AL. (1998) relates to a method for large scale purification of Japanese Encephalitis vaccine in vero cells. The JE vaccine in vero cells is purified by zonal centrifugation at non-continuous sucrose gradients.

TAKEGAMI ET AL. relates to the use of the antiviral drug furanonaphthoquinone-derivative, 5-hydroxy-2-(1-hydroxyethyl)naphtho[2,3-b] (FNQ3) against Japanese Encephalitis virus (JEV).

HUIYING ET AL. (1995) relates to a P3 strain of Japanese Encephalitis virus adapted in Vero cells.The immunogenicity of the cells was weaker after 10 passages. The virus growing in Vero cells with less than 10 passages could be used as seed virus for production of JE vaccine instead of virus prepared from mouse brain.

C. Analysis

According to the M.P.E.P. § 2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference".

1. Rejection over Huiying et al. (1998) or Takegami et al.

Huiying et al. (1998) is concerned with providing a vaccine purified by zonal centrifugation. The teaching nowhere shows an inactivation step. Since Huiying et al. (1998) fail to describe a step of inactivation followed by a step of purification by physical means, the reference does not anticipate the present claims.

Takegami et al. fail to describe a step of inactivation, much less inactivation followed by a step of purification by physical means. In fact, Takegami et al. are concerned with using the active virus for experimentation with an antiviral drug against JEV.

Takegami et al. describe the use of FNQ3 as an antiviral inhibitor against JEV. Takegami et al. incubate FNQ3 with purified JEV (page 38, section 2.3). The Examiner cites this as a teaching of Vero cells infected with JEV that were inactivated and purified. Applicants respectfully disagree. Section 2.2 of Takegami et al. describes the preparation of the Vero cells adsorbed with JEV. The process includes (i) adsorption with JEV for 1 hour at ten m.o.i.; (ii) removal of the virus solution; (iii) culturing the cells in MEM containing 5% FCS for 24 hours; (iv) titrating by the plaque method; (v) harvesting the infected cells; (vi) centrifugation; and (vii) suspending the cell pellets in TE buffer.

Nowhere does Takegami et al. describe a step of inactivation, much less inactivation followed by a step of purification by physical means. In fact, Takegami et al. is concerned with using the active virus for experimentation with an antiviral drug against JEV.

Accordingly, Applicants respectfully request withdrawl of the rejections under 35 U.S.C. §102(a).

2. Rejection over Huiying et al. (1995)

Huiying et al. (1995) fail to disclose an inactivating step, much less inactivation followed by a step of purification by physical means. Huiying et al. (1995) describe a strain of Japanese

Encephalitis virus prepared by attenuating the virus by passage through Vero cells. The attenuated JEV is described as able to be used as seed virus for the production of vaccines.

Accordingly, Applicants respectfully request withdrawl of the rejection under 35 U.S.C. §102(b).

V. Rejection under 35 U.S.C. §103

Claims 1-7 and 9-16 were rejected under 35 U.S.C. §103 as being obvious over Huiying et al. (1998) or Takegami et al. or Huiying et al. (1995) in view of Kotaro et al.

A. The Present Invention

The present invention is described above.

B. The Prior Art

HUIYING ET AL. (1998) is described above.

TAKEGAMI ET AL. is described above.

HUIYING ET AL. (1995) is described above.

KOTARO ET AL. describe a production process of surface antigen protein of Japanese encephalitis virus useful as a prophylactic medicine or diagnostic agent. An expression vector into which the whole or part of cDNA coding for the surface protein (E protein) of Japanese encephalitis virus is incorporated together with the whole or a part of cDNA coding for the matrix protein of the virus, or the whole or a part of cDNA coding for the prematrix protein of the virus, or a part of the core protein of the virus, is introduced into the host mammalian cells to effect efficient production of E (envelope) protein.

C. Analysis

According to the MPEP § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art,

to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

As noted above, Huiying et al. (1998), Takegami et al. and Huiying et al. (1995), alone or in combination, fail to teach or suggest preparation of an inactivated virus particle including a step of inactivation followed by a step of purification by physical means.

The teachings in Kotaro et al. when combined with Huiying et al. (1998), Takegami et al. or Huiying et al. (1995) do not make up for these deficiencies. Kotaro et al. is not concerned with an inactivated virus particle prepared from a culture of cells infected with Japanese encephalitis viruses. Kotaro et al. makes no mention of a process comprising the steps of inactivation followed by a step of purification by physical means. The Examiner cites Kotaro et al. to show use in the art of purified immunogens in a diagnostic kit. Applicants respectfully disagree. Kotaro et al. merely teaches introducing an expression vector in which cDNA encoding the surface antigen protein of Japanese encephalitis virus is incorporated with the cDNA encoding the matrix protein or the cDNA of the prematrix protein or a part of the core protein into the host mammalian cells to effect efficient production fo E protein. Kotaro et al. state that the expression vector is useful as a prophylactic medicine or diagnostic agent, but makes no mention of the use of a diagnostic kit or of diagnostic kits containing purified immunogens.

Thus, nowhere do any of the references, taken alone or in combination, show or suggest an inactivated virus particle prepared from a culture of cells infected with Japanese encephalitis viruses including a step of inactivation followed by a step of purification by physical means.

In view of the above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

VI. Conclusion

In view of the foregoing, Applicants submit that the claims pending in the application comply with the requirements of 35 U.S.C. §112 and patentably define over the prior art. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4410.

Respectfully submitted,

Jacqueline F. Mahoney

Date: February 27, 2002

Jacqueline F. Mahoney
Registration No. 48,390

Correspondence Address:
Customer No. 22918
(650) 838-4300

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The present invention provides a novel inactivated virus particle and a reinforced immunogen which have a reinforced titer about twice to about 10 times that of a conventional vaccine, as well as a method for producing the same. The inactivated virus particle is produced by inactivating and then purifying a culture by physical means. The inactivated virus particle of the present invention is useful in a diagnostic agent for infectious disease caused by a group of Japanese encephalitis virus.

1. (Amended) An inactivated virus particle, as a reinforced immunogen, prepared from a culture of cells infected with virus belonging to a group of Japanese encephalitis viruses, wherein the process of preparation comprises a step of inactivation followed by a step of purification by physical means, wherein a neutralizing antibody titer of the anti-serum obtained by immunization with the virus particles is about twice to about 10 times the neutralizing antibody titer of the anti-serum obtained by immunization with inactivated virus particles prepared from virus cultured in mouse brain.

2. (Amended) A method for producing an inactivated virus particle, comprising culturing virus belonging to a group of Japanese encephalitis viruses in a cell line, [as well as] inactivating [and purifying] the cell culture and then purifying the virus by physical means, wherein a neutralizing antibody titer of the anti-serum obtained by immunization with the virus particles is about twice to about 10 times the neutralizing antibody titer of the anti-serum obtained by immunization with inactivated virus particles prepared from virus cultured in mouse brain.

5. (Amended) The method of claim 2, wherein the inactivating is conducted at a temperature in a range of about 4°C to about 10°C[40°C to about 100°C].

13. (Amended) The inactivated virus particle of claim [11]1 wherein said cells are inactivated at a temperature in a range of about 4°C to about 10°C[40°C to about 100°C].